FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6274138	B1	20010814	US 1997-922957	19970903
US 2002086006	A1	20020704	US 2001-915694	20010725
PRIORITY APPLN. INFO.:			US 1997-922957	A3 19970903

AB This invention relates to nucleic acid and amino acid sequences of a human mitochondrial malate dehydrogenase (MT-MDH). Nucleic acids encoding the MT-MDH of the present invention were first identified in Incyte Clone 11587 from the human peripheral promonocyte cell line cDNA library (THP1PLB01) using a computer search for amino acid sequence alignments. MT-MDH is 294 amino acids in length and has chemical and structural homol. with murine mitochondrial malate dehydrogenase and porcine mitochondrial malate dehydrogenase. Northern anal. shows the expression of this sequence in various libraries. The invention also provides expression vectors, host cells, agonists, antibodies and antagonists. The invention also provides methods for treating disorders associated with expression of MT-MDH.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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NEWS 1		Web Page for STN Seminar Schedule - N. America
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NEWS 3	JUL 02	SCISEARCH enhanced with complete author names
NEWS 4	JUL 02	CHEMCATS accession numbers revised
NEWS 5	JUL 02	CA/CAplus enhanced with utility model patents from China
NEWS 6	JUL 16	CAplus enhanced with French and German abstracts
NEWS 7	JUL 18	CA/CAplus patent coverage enhanced
NEWS 8	JUL 26	USPATFULL/USPAT2 enhanced with IPC reclassification
NEWS 9	JUL 30	USGENE now available on STN
NEWS 10	AUG 06	CAS REGISTRY enhanced with new experimental property tags
NEWS 11	AUG 06	BEILSTEIN updated with new compounds
NEWS 12	AUG 06	FSTA enhanced with new thesaurus edition
NEWS 13	AUG 13	CA/CAplus enhanced with additional kind codes for granted patents
NEWS 14	AUG 20	CA/CAplus enhanced with CAS indexing in pre-1907 records
NEWS 15	AUG 27	Full-text patent databases enhanced with predefined patent family display formats from INPADOCDB
NEWS 16	AUG 27	USPATOLD now available on STN
NEWS 17	AUG 28	CAS REGISTRY enhanced with additional experimental spectral property data
NEWS 18	SEP 07	STN AnaVist, Version 2.0, now available with Derwent World Patents Index
NEWS 19	SEP 13	FORIS renamed to SOFIS
NEWS 20	SEP 13	INPADOCDB enhanced with monthly SDI frequency
NEWS 21	SEP 17	CA/CAplus enhanced with printed CA page images from

1967-1998
NEWS 22 SEP 17 CAplus coverage extended to include traditional medicine patents
NEWS 23 SEP 24 EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS 24 OCT 02 CA/CAplus enhanced with pre-1907 records from Chemisches Zentralblatt

NEWS EXPRESS 19 SEPTEMBER 2007: CURRENT WINDOWS VERSION IS V8.2, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 SEPTEMBER 2007.

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FILE 'HOME' ENTERED AT 07:57:09 ON 16 OCT 2007

=> file reg
COST IN U.S. DOLLARS SINCE FILE ENTRY 0.21 TOTAL SESSION 0.21
FULL ESTIMATED COST

FILE 'REGISTRY' ENTERED AT 07:57:31 ON 16 OCT 2007
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 15 OCT 2007 HIGHEST RN 950725-14-1
DICTIONARY FILE UPDATES: 15 OCT 2007 HIGHEST RN 950725-14-1

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TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

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REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=> s
KAKAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYFSTPLLLGKKGIEKNLGIGKVSSFEEKMISDAIPE
LKASIKKGEDFVKTLK/sqep
2 KAKAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYFSTPLLLGKKGIEKN
LGIGKVSSFEEKMISDAIPELKASIKKGEDFVKTLK/SQEP
68052 SQL=100

L1 2 KAKAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYFSTPLLLGKKGIEKN
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(KAKAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYFSTPLLLGKKGI
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=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	7.70	7.91

FILE 'CAPLUS' ENTERED AT 07:57:45 ON 16 OCT 2007
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FILE COVERS 1907 - 16 Oct 2007 VOL 147 ISS 17
FILE LAST UPDATED: 15 Oct 2007 (20071015/ED)

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http://www.cas.org/infopolicy.html

=> s l1
L2 2 L1

=> d ibib 1-2

L2 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:681680 CAPLUS
DOCUMENT NUMBER: 141:200162
TITLE: Mitochondrial malate dehydrogenase DNA fragmentation activator fragment and related conjugated proteins and antibodies for cancer therapy
INVENTOR(S): Wright, Susan C.; Larrick, James W.; Nock, Steffen R.; Wilson, David S.
PATENT ASSIGNEE(S): Palo Alto Institute of Molecular Medicine, USA
SOURCE: PCT Int. Appl., 225 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004070012	A2	20040819	WO 2004-US2974	20040202
WO 2004070012	A3	20060330		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

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            MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
            GQ, GW, ML, MR, NE, SN, TD, TG, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
    AU 2004209644         A1    20040819    AU 2004-209644          20040202
    CA 2514841            A1    20040819    CA 2004-2514841         20040202
    US 2004191843         A1    20040930    US 2004-770668          20040202
    EP 1590440            A2    20051102    EP 2004-707424          20040202
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
    JP 2006522021         T     20060928    JP 2006-503266          20040202
PRIORITY APPLN. INFO.:                      US 2003-444191P     P   20030203
                                            US 2003-460855P     P   20030408
                                            US 2004-770668      A   20040202
                                            WO 2004-US2974      W   20040202

L2   ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        2004:681539  CAPLUS
DOCUMENT NUMBER:         141:212819
TITLE:                   Compounds useful in coating stents to prevent and
                         treat stenosis and restenosis
INVENTOR(S):             Wang, Yuqiang; Larrick, James W.; Wright, Susan C.
PATENT ASSIGNEE(S):      Medlogics Device Corporation, USA
SOURCE:                  PCT Int. Appl., 63 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

    PATENT NO.            KIND   DATE        APPLICATION NO.         DATE
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    WO 2004069201         A2     20040819    WO 2004-US3143          20040203
    WO 2004069201         A3     20050519
        W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
            CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
            GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
            LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI
        RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
            BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU,
            MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
            GQ, GW, ML, MR, NE, SN, TD, TG
    US 2007037739         A1     20070215    US 2006-544241          20060103
PRIORITY APPLN. INFO.:                      US 2003-444391P     P   20030203
                                            WO 2004-US3143      W   20040203
OTHER SOURCE(S):         MARPAT 141:212819


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COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 3.77      11.68

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NEWS 7	JUL 18	CA/CAplus patent coverage enhanced
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NEWS 10	AUG 06	CAS REGISTRY enhanced with new experimental property tags
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NEWS 13	AUG 13	CA/CAplus enhanced with additional kind codes for granted patents
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NEWS 16	AUG 27	USPATOLD now available on STN
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NEWS 18	SEP 07	STN AnaVist, Version 2.0, now available with Derwent World Patents Index
NEWS 19	SEP 13	FORIS renamed to SOFIS
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NEWS 22	SEP 17	CAplus coverage extended to include traditional medicine patents
NEWS 23	SEP 24	EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS 24	OCT 02	CA/CAplus enhanced with pre-1907 records from Chemisches Zentralblatt

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FILE 'HOME' ENTERED AT 07:59:55 ON 16 OCT 2007

=> file pctfull
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.42	0.42

FILE 'PCTFULL' ENTERED AT 08:01:14 ON 16 OCT 2007
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FILE LAST UPDATED: 16 OCT 2007 <20071016/UP>
MOST RECENT UPDATE WEEK: 200741 <200741/EW>
FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

>>> PREDEFINED PATENT FAMILY FORMATS CFAM AND FAM FROM THE INPADOCDB DATABASE NOW AVAILABLE <<<

=> s WO0166689/pn
L1 0 WO0166689/PN
(WO166689/PN)

=> s WO 0166689/pn
L2 0 WO 0166689/PN
(WO166689/PN)

=> s WO200166689/pn
L3 1 WO200166689/PN
(WO2001066689/PN)

=> d ibib

L3 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2007 Univentio on STN
ACCESSION NUMBER: 2001066689 PCTFULL ED 20020822
TITLE (ENGLISH): NOVEL NUCLEIC ACIDS AND POLYPEPTIDES
TITLE (FRENCH): NOUVEAUX ACIDES NUCLEIQUES ET POLYPEPTIDES
INVENTOR(S): TANG, Y., Tom;
LIU, Chenghua;
ASUNDI, Vinod;
XU, Chongjun;
WEHRMAN, Tom;
REN, Feiyan;
MA, Yunqing;
ZHOU, Ping;
ZHAO, Qing, A.;
YANG, Yonghong;
DRMANAC, Radoje, T.;
ZHANG, Jie;
CHEN, Rui-hong;
XUE, Aidong, J.;
WANG, Jian-Rui
PATENT ASSIGNEE(S): HYSEQ, INC.;
TANG, Y., Tom;
LIU, Chenghua;
ASUNDI, Vinod;
XU, Chongjun;
WEHRMAN, Tom;
REN, Feiyan;
MA, Yunqing;

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                        ZHOU, Ping;
                        ZHAO, Qing, A.;
                        YANG, Yonghong;
                        DRMANAC, Radoje, T.;
                        ZHANG, Jie;
                        CHEN, Rui-hong;
                        XUE, Aidong, J.;
                        WANG, Jian-Rui
DOCUMENT TYPE:          Patent
PATENT INFORMATION:
                        NUMBER              KIND     DATE
                        ---------------------------------
                          WO 2001066689        A2 20010913
DESIGNATED STATES
       W:               AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU
                        CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN
                        IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK
                        MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM
                        TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD
                        SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY
                        DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF
                        CG CI CM GA GN GW ML MR NE SN TD TG
PRIORITY INFO.:         US 2000-09/519,705       20000307
                        US 2000-09/574,454       20000519
                        US 2000-09/596,193       20000617
                        US 2000-09/616,847       20000714
                        US 2000-09/665,363       20000919
                        US 2000-09/693,267       20001020
APPLICATION INFO.:      WO 2001-US4942        A  20010305


=> d his

     (FILE 'HOME' ENTERED AT 07:59:55 ON 16 OCT 2007)

     FILE 'PCTFULL' ENTERED AT 08:01:14 ON 16 OCT 2007
L1             0 S WO0166689/PN
L2             0 S WO 0166689/PN
L3             1 S WO200166689/PN

=> s l3 and fragment?
         142984 FRAGMENT?
L4             1 L3 AND FRAGMENT?

=> d ibib kwic

L4     ANSWER 1 OF 1     PCTFULL   COPYRIGHT 2007 Univentio on STN
ACCESSION NUMBER:       2001066689 PCTFULL  ED 20020822
TITLE (ENGLISH):        NOVEL NUCLEIC ACIDS AND POLYPEPTIDES
TITLE (FRENCH):         NOUVEAUX ACIDES NUCLEIQUES ET POLYPEPTIDES
INVENTOR(S):            TANG, Y., Tom;
                        LIU, Chenghua;
                        ASUNDI, Vinod;
                        XU, Chongjun;
                        WEHRMAN, Tom;
                        REN, Feiyan;
                        MA, Yunqing;
                        ZHOU, Ping;
                        ZHAO, Qing, A.;
                        YANG, Yonghong;
                        DRMANAC, Radoje, T.;
                        ZHANG, Jie;
                        CHEN, Rui-hong;
                        XUE, Aidong, J.;
                        WANG, Jian-Rui
```

PATENT ASSIGNEE(S): HYSEQ, INC.;
TANG, Y., Tom;
LIU, Chenghua;
ASUNDI, Vinod;
XU, Chongjun;
WEHRMAN, Tom;
REN, Feiyan;
MA, Yunqing;
ZHOU, Ping;
ZHAO, Qing, A.;
YANG, Yonghong;
DRMANAC, Radoje, T.;
ZHANG, Jie;
CHEN, Rui-hong;
XUE, Aidong, J.;
WANG, Jian-Rui

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001066689	A2	20010913

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU
CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN
IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK
MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM
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SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY
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CG CI CM GA GN GW ML MR NE SN TD TG

PRIORITY INFO.: US 2000-09/519,705 20000307
US 2000-09/574,454 20000519
US 2000-09/596,193 20000617
US 2000-09/616,847 20000714
US 2000-09/665,363 20000919
US 2000-09/693,267 20001020

APPLICATION INFO.: WO 2001-US4942 A 20010305

PI WO 2001066689 A2 20010913

DETD . . . at least 90% identity to an identifying sequence of SEQ ID NO: 1-1 88, or 377-564 or a degenerate variant or fragmentthereof. The identifying sequence can be 1 00 base pairs in length.

The term expression modulating fragment, EMF, means a series of nucleotides which modulates the expression of an operably linked ORF or another EMF.

. . .

EMF. EMFs include, but are not limited to, promoters, and promoter modulating sequences (inducible elements). One class of EMFs are nucleic acid fragments which induce the expression of an operably linked ORF in response to a specific regulatory factor or physiological event.

. . .

in the sequences provided herein is substituted with U (uracil). Generally, nucleic acid segments provided by this invention may be assembled from fragments of the genome and short oligonucleotide linkers, or from a series of oligonucleotides, or from individual nucleotides, to provide a synthetic. . .

The tenns oligonucleotide fragment or a polynucleotide

fragment, portion, or
11segment or probe or primer are used interchangeably and refer to a sequence of nucleotide
residues which are at least. . . least about 9 nucleotides, more preferably at least about I 1 nucleotides and
most preferably at least about 17 nucleotides. The fragment is preferably less than about 500
nucleotides, preferably less than about 200 nucleotides, more preferably less than about I 00
nucleotides, more. . . 50 nucleotides, more preferably from about 17 to 30
7
nucleotides and most preferably from about 20 to 25 nucleotides. Preferably the fragments can
be used in polyrnerase chain reaction (PCR), various hybridization procedures or microarray
procedures to identify or amplify identical or related parts of mRNA or DNA molecules. A
fragment or segment may uniquely identify each polynucleotide sequence of the present
invention. Preferably the fragment comprises a sequence substantially similar to any one of SEQ
ID NOs - I- 1 88, or 3 77
Probes may,. . .

The terms polypeptide or peptide or amino acid sequence refer to an oligopeptide,
peptide, polypeptide or protein sequence or fragment thereof and to naturally occurring or
synthetic molecules. A polypeptide fragment, portion, or segment is a stretch of amino
,15 acid residues of at least about 5 amino acids, preferably at least.
. .

I 0 As used herein, an uptake modulating fragment, UMF, means a series of nucleotides
which mediate the uptake of a linked DNA fragment into a cell. UMFs can be readily identified
using known UMFs as a target sequence or target motif with the computer-based. . .
. . .
obtained from one or more public databases, such as dbEST, gbpri, and UniGene. The EST sequences can provide identifying sequence information,
representative fragment or segment information, or novel segment infori-nation for the full-length
gene.

Included within the scope of the nucleic acid sequences of the invention a-re nucleic acid
sequence fragments that hybridize under stringent conditions to any of the nucleotide sequences
of SEQ ID NO: I- 1 8 8, or 3 77-564, or complements thereof, which fragment is. greater than about
15
nucleotidcs, preferably 7 nucleotides, more preferably greater than 9 nucleotides and most
preferably greater than 17 nucleotides. Fragments of, e.g. 15, 17, or 20 nucleotides or more that
are selective for (i.e. specifically hybridize to any one of the. . .
. . .
0 variations can be routinely determined by comparing the sequenceprovided in SEQ ID NO: 1-1 88,
or 3 :)77-564, a representative fragment thereof, or a nucleotide sequence at least 90% identical,

preferably 95% identical, to SEQ ID NO: I- 1 8 8, or. . .
. . .
region in the template DNA can generate the desired
amino acid variant. PCR amplification results in a population of product
DNA fragments that
differ from the polynucleotide template encoding the polypeptide at the
position specified by the
primer. The product DNA fragments replace the corresponding
region in the plasmid and this
3 0 gives a polynucleotide encoding the desired amino acid variant.
. . .
constructs comprising a nucleic acid
having any of the nucleotide sequences of SEQ ID NO: 1-1 88, or '377-564
or a fragment thereof
or any other polynucleotides of the invention. In one embodiment, the
recombinant constructs of
the present invention comprise a vector, such. . . into which a
nucleic
acid having any of the nucleotide sequences of SEQ ID NO: 1-1 88, or
377-564 or a fragment
thereof is inserted, in a forward or reverse orientation. In the case of
a vector comprising one of
the ORFs of the. . .
. . .
complementary to the nucleic acid molecule comprising the nucleotide
sequence of SEQ ID NO: I- IS 8, or 3 77-564, or fragments,
analogs or derivatives thereof. An
antisense nucleic acid comprises a nucleotide sequence that is
complementary to a sense
nucleic acid encoding a. . . 25,
50, 100, 250 or 500 nucleotides or an entire coding strand, or to only a
portion thereof. Nucleic
acid molecules encoding fragments, homologs, derivatives and
analogs of a protein of any of
20
SEQ ID NO: 189-376, or 565-752 or antisense nucleic acids complementary.
. .
. . .
one of the
polynucleotides of the invention, can be used in conventional manners to
produce the gene
product encoded by the isolated fragment (in the case of an
ORF) or can be used to produce a
heterologous protein under the control of the EMF.
. . .
variants may have a similar, increased, or decreased
activity compared to polypeptides comprising SEQ ID NO: 189-3 76, or 5
65
Fragments of the proteins of the present invention which are
capable of exhibiting
biological activity are also encompassed by the present invention.
Fragments of the protein may
be in linear form or they may be cyclized using known methods, for
example, as described in. . .

Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein
by reference. Such
fragments may be fused to carrier molecules such as
immunoglobulins for many purposes,
including increasing the valeney of protein binding sites.

The present invention fartlier provides isolated polypeptides encoded by
the nucleic acid
fragments of the present invention or by degenerate variants
of the nucleic acid fragments of the

present invention. By degenerate variant is intended nucleotide fragments which differ from a
nucleic acid fragment of the present invention (e.g., an ORF)
by nucleotide sequence but, due to
the degeneracy of the genetic code, encode an identical polypeptide sequence. Preferred nucleic
acid fragments of the present invention are the ORFs that
encode proteins.

. . .
with proteins may possess biological properties
in common therewith, including protein activity. This technique is particularly useful in
producing small peptides and fragments of larger polypeptides. Fragments are useful, for
example, in generating antibodies against the native polypeptide. Thus, they may be employed
as biologically active or immunological substitutes. . .

. . .
and
Practice, Springer-Verlag (1994); Sambrook, et al., in Molecular Cloning: A Laboratory
Manual; Ausubel et al., Current Protocols in Molecular Biology. Polypeptide fragments that
29
retain biological/immunological activity include fragments comprising greater than about I 00
amino acids, or greater than about 200 amino acids, and
fragments that encode specific protein
domains.

p
Other fragments and derivatives of the sequences of proteins which would be expected to
retain protein activity in whole or in part and. . .

. . .
is defined in accordance with the present invention as an isolated protein.
31
The polypeptides of the invention include analogs (variants). This embraces fragments,
as well as peptides in which one or more arnino acids has been deleted, inserted, or substituted.

A chimeric or fusion protein of the invention can be produced by standard recombinant
DNA techniques. For example, DNA fragments coding for the different polypeptide sequences
are ligated together in-frame in accordance with conventional techniques, e.g., by employing
blunt-ended or stagger-ended termini. . .

Alternatively, PCR amplification of gene fragments can be carried out using anchor primers that
give rise to complementary overhangs between two consecutive gene fragments that can
subsequently be annealed and reamplified to generate a chimeric gene sequence (see, for
example, Ausubel et al. (eds.) CURRENT PROTOCOLS. . .

. . .
gene products, either at the level of target gene/protein expression or target protein
activity. Such modulators include polypeptides, analogs, (variants)] including fragments and
fusion proteins, antibodies and other binding proteins; chemical compounds that directly or

I 0 indirectly activate or inhibit the polypeptides of. . .
. . .
screening of potential peptide or small molecule inhibitors of the relevant
receptor/ligand interaction. A protein of the present invention (including, without limitation,
fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand
interactions.

4 13 DRUG SCREENING
This invention is particularly useful for screening chemical compounds by using the
novel polypeptides or binding fragments thereof in any of a variety of drug screening techniques.

The polypeptides or fragments employed in such a test may either be free in solution, affixed to a
solid support, borne on a cell surface. . . of drug screening utilizes eukaryotic or prokaryotic host cells which axe stably transformed with recombinant
nucleic acids expressing the polypeptide or a fragment thereof. Drugs are screened against such
55
transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can
be used for standard binding assays. One may measure, for example, the formation of complexes
between polypeplides of the invention or fragments and the agent being tested or examine the
diminution in complex formation between the novel polypeptides and an appropriate cell line,
which. . .
. . .
DNA, and identifying the presence of the
polymorphism in the DNA. For example, PCR may be used to amplify an appropriate fragment
of genomic DNA which may then be sequenced. Alternatively, the DNA may be subjected to
allele-specific oligonucleotide hybridization (in which appropriate oligonucleotides. . .

In addition, traditional restriction fragment length
polymorphism analysis (using restriction
enzymes that provide differential digestion of the genomic DNA depending on the presence or
absence of the. . .

4.11 THERAPEUTIC METHODS
The compositions (including polypeptide fragments, analogs, variants and antibodies or
other binding partners or modulators including antisense polynucleotides) of the invention have
numerous applications in a variety. . .

4.13 ANTIBODIES
Also included in the invention are antibodies to proteins, or fragments of proteins of the
invention. The term antibody as used herein refers to imm-unoglobulin molecules and
immunologically active portions of immunoglobulin (1g). . . binds (immunoreacts with) an antigen. Such antibodies
include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, Fab, Fab, and F(ab')2
fragments, and an Fab expression library. In general, an

antibody molecule obtained from
humans relates to any of the classes IgG, IgM,. . .

An isolated related protein of the invention may be intended to serve as an antigen, or a
portion or fragment thereof, and additionally can be used as an immunogen to generate
antibodies that immunospecifically bind the antigen, using standard techniques for polyclonal
and monoclonal antibody preparation. The full-length protein can be used or, alternatively, the
invention provides antigenic peptide fragments of the antigen for use as immunogens. An
antigenic peptide fragment comprises at least 6 amino acid residues of the amino acid sequence
of the full length protein, such as the amino. . . such that an antibody raised against the peptide
forms a specific immune complex with the full length protein or with any fragment that contains
the epitope. Preferably, the antigenic peptide comprises at least IO amino acid residues, or at
least 15 amino acid residues,. . .

Antibodies that are specific for one or more domains within an antigenic protein, or derivatives,
fragments, analogs or homologs thereof, are also provided herein.

A protein of the invention, or a derivative, fragment, analog, homolog or ortholog
thereof, may be utilized as an immunogen in the generation of antibodies that
immunospecifically bind these protein components.

. . .
be used for the producti'on of polyclonal or
I 0 monoclonal antibodies directed against a protein of the invention, or against derivatives,
fragments, analogs homologs or orthologs thereof (see, for example, Antibodies: A Laboratory
Manual, Harlow E, and Lane .D, 1988, Cold Spring Harbor. . .

The immunizing agent will typically include the protein antigen, a fragment thereof or a fusion
protein thereof. Generally, either peripheral blood lymphocytes are used if cells of human origin
are desired, or spleen. . .

. . .
without engendering an immune response by the human against the administered
immunoglobulin. Humanized forms of antibodies are chimeric immunoglobulins,
immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')2 or other antigen-
binding subsequences of antibodies) that are principally comprised of the sequence. . .

. . .
selecting an antibody that binds
immunospecifically to the relevant epitope with high affinity, are disclosed in PCT publication 4 5 Fab FRAGMENTS AND SINGLE CHAIN ANTIBODIES
According to the invention, techniques can be adapted for the production of single-chain
antibodies specific to an antigenic. . .

. . .
Fab expression libraries (see e.g.,

Huse, et al., 1989 Science 246: 1275-128 1) to allow rapid and effective identification of monoclonal Fab fragments with the desired specificity for a protein or derivatives, fragments, analogs or homologs thereof Antibody fragments that contain the idiotypes to a protein antigen may be produced by techniques known in the art including, but not limited to: (i) an F(&)2 fragment produced by pepsin digestion of an antibody molecule; (ii) an Fab fragment generated by reducing the disulfide bridges of an F(,,bl)2 fragment; (iii) an Fab fragment generated by the treatment of the antibody molecule with papain and a reducing agent and (iv) F, fragments.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g.

F(ab')2 bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al., Science 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F(ab')2 fragments. These 5 fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to 81 stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with. . .

Additionally, Fab' fragments can be directly recovered from E. coli and chemically coupled to form bispecific antibodies. Shalaby et al., J. ENP. Med. 175:217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')2 molecule, Each Fab' fragment I 0 was separately secreted from E. coli and subjected to directed chemical coupling in vitro to form the bispecific antibody. The. . .

Various techniques for making and isolating bispecific antibody fragments directly from 5 recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et. . . technology described by Hollinger et al., Proc. Nall. Acad. Sci. USA 90:6444-6449 (1993) has provided an alternative mechanism for making bispecific antibody fragments . The fragments comprise a heavy-chain variable domain (VH) connected to a light-chain variable domain (VL) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the VIj and VL domains of one fragment are forced to pair with the complementary VL and VH domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been

reported. See, Gruber et al., J. Immunol. 152:5368 (1994).
. . .
a
cytotoxic agent such as a chemotherapeutic agent, toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a 3S radioconjugate).

J,
Chemotherapeutic agents useful in the generation of such inimunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from Pseudomonas aeruginosa), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins,. . .

By providing any of the nucleotide sequences SEQ ID NO: I- 1 8 8, or 3 77-564 or a representative fragment thereof, or a nucleotide sequence at least 95% identical to any of the nucleotide sequences of SEQ ID NO: 1-188, or. . . a Sybase system is used to identify open reading frames (ORFs) within a micleic acid sequence. Such ORFs may be protein encoding fragments and may be useful in producing commercially important proteins such as enzymes used in fermentation reactions and in the production of. . .
. . .
sequence or target structural motif with the sequence information stored within the data storage means. . Search means are used to identify
fragments or regions of a known sequence which match a particular target sequence or target motif A variety of known algorithms are. . . acids, more preferably from about 'JO to I 00 nucleotide residues. However, it is well recognized that searches for commercially important fragments, such as sequence fragments involved in gene expression and protein processing, may be of shorter length.

4.15 TRIPLE HELIX FORMATION
In addition, the fragments of the present invention, as broadly described, can be used to control gene expression through triple helix formation or antisense DNA. . .

4,21 PREPARATION OF NUCLEIC ACID FRAGMENTS
The nucleic acids may be obtained from any appropriate source, such as cDNAs, genomic DNA, chromosomal DNA, microdissected chromosome bands, cosmid or. . .

DNA fragments may be prepared as clones in M133, plasmid or lambdavectors and/or prepared directly from genomic DNA or cDNA by PCR or. . .

The nucleic acids would then be fragmented by any of the methods known to those of skill in the art including, for example, using restriction enzymes as described. . .
. . .

to the cell. The results of these
studies indicate that low-pressure shearing is a useftil alternative
to'sonic and enzymatic DNA
3 0 fragmentationmethods.

One particularly suitable way for fragmenting DNA is
contemplated to be that using the two
base recognition endonuclease, CviJI, described by Fitzgerald et al. (I
992) Nucleic. . .
. . .
leave blunt ends. Atypical reaction conditions, which alter the
specificity of
this enzyme (CviJl* *), yield a quasi-random distribution of DNA
fragments form the small
molecule pUC 1 9 (268 8 base pairs). Fitzgerald et al. (I 992)
quantitatively evaluated the
randomness of this fragmentation strategy, using a CviJl* *
digest of pUC 1 9 that was size
fractionated by a rapid gel filtration method and. . . and
I 0 PuGCPu, in addition to PuGCPy sites, and that new sequence data is
accumulated at a rate
consistent with random fragmentation.
. . .
repair, chemical extraction, or agarose gel
1 5 electrophoresis and elution are needed
Irrespective of the manner in which the nucleic acid fragments
are obtained or prepared, it is
important to denature the DNA to give single stranded pieces available
for hybridization. This is
achieved. . . DNA solution for 2-5 minutes at 80-90'C. The solution
is then cooled
quickly to 2'C to prevent renaturation of the DNA fragments
before they are contacted with the
chip. Phosphate groups must also be removed from genomic DNA by methods
known in the. . .

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	18.69	19.11

STN INTERNATIONAL LOGOFF AT 08:06:47 ON 16 OCT 2007